

In Vitro Activity of Tigecycline Against Pathogens From Switzerland, Sweden, and The Netherlands - T.E.S.T. Program 2006

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REVISED ABSTRACT

Background: Tigecycline (TIG), a new glycycline, has been shown to have potent broad spectrum activity against most commonly encountered species responsible for community- and hospital-acquired infections. The T.E.S.T. program determined the in vitro activity of TIG and 10 comparators against respective gram positive/negative species. Isolates were collected during 2004 to 2006. **Methods:** A total of 570 clinically significant isolates from Switzerland, Sweden and The Netherlands were analyzed in this survey. Isolates were identified to the species level at the participating sites and confirmed by the central laboratory. MICs were determined by each site using supplied broth microdilution panels and interpreted according to CLSI guidelines. **Results:** Selected pathogens tested against tigecycline are shown in the table below:

Organism Name	Drug	%SUS ^a		%INT		%RES		MIC (mcg/ml)	
		%SUS ^a	%INT	%RES	MIC ₅₀	MIC ₉₀	MIC ₉₅		
<i>E. coli</i> and <i>Necisseria</i> spp. (n=148)	Tigecycline	100	0	0	0.12	0.12			
	Amikacin	100	0	0	2	4			
	AmoxClav	99	8.2	2.7	4	16			
	Ampicillin	98.9	0	41.1	4	>32			
	Cefepime	98.9	1.4	2.7	>0.5	>0.5			
	Ceftazidime	98.6	1.4	0	>8	>8			
	Ceftriaxone	94.5	0	5.5	>0.06	0.12			
	Imipenem	100	0	0	0.25	0.25			
	Levofloxacin	87.7	6.8	5.5	0.03	4			
	Minocycline	91.8	6.8	1.4	1	4			
PipTazo	97.3	2.7	0	0.5	2				
<i>K. pneumoniae</i> (n=42)	Tigecycline	95.2	2.4	2.4	0.25	0.5			
	Amikacin	100	0	0	1	2			
	AmoxClav	97.6	2.4	0	2	8			
	Ampicillin	0	33.3	66.7	32	>32			
	Cefepime	100	0	0	>0.5	>0.5			
	Ceftazidime	100	0	0	>8	>8			
	Ceftriaxone	100	0	0	>0.06	>0.06			
	Imipenem	100	0	0	0.25	0.5			
	Levofloxacin	100	0	0	0.03	0.25			
	Minocycline	88.1	0	11.9	1	16			
PipTazo	97.6	0	2.4	1	2				
<i>K. oxytoca</i> (n=33)	Tigecycline	100	0	0	0.25	0.5			
	Amikacin	100	0	0	1	2			
	AmoxClav	100	0	0	2	4			
	Ampicillin	0	21.2	78.8	>32	>32			
	Cefepime	97	3	0	>0.5	>0.5			
	Ceftazidime	100	0	0	>8	>8			
	Ceftriaxone	97	0	3	>0.06	0.25			
	Imipenem	100	0	0	0.25	0.5			
	Levofloxacin	100	0	0	0.03	0.06			
	Minocycline	100	0	0	1	2			
PipTazo	93.9	6.1	0	1	4				
<i>S. aureus</i> ^b (n=75)	Tigecycline	100	0	0	0.25	0.5			
	Amikacin	100	0	0	2	4			
	AmoxClav	0	0	0	2	4			
	Ampicillin	0	100	>32	>32	>32			
	Cefepime	100	0	0	>0.5	>0.5			
	Ceftazidime	100	0	0	>8	>8			
	Ceftriaxone	97	0	3	>0.06	0.25			
	Imipenem	100	0	0	0.25	0.5			
	Levofloxacin	100	0	0	0.03	0.06			
	Minocycline	100	0	0	1	2			
PipTazo	93.9	6.1	0	1	4				
<i>E. cloacae</i> (n=40)	Tigecycline	100	0	0	0.5	0.5			
	Amikacin	100	0	0	2	2			
	AmoxClav	2.5	2.5	95	>32	>32			
	Ampicillin	0	5	95	>32	>32			
	Cefepime	100	0	0	>0.5	2			
	Ceftazidime	95	2.5	12.5	>8	>32			
	Ceftriaxone	87.5	7.5	5	0.25	16			
	Imipenem	100	0	0	0.5	0.5			
	Levofloxacin	100	0	0	0.03	0.06			
	Minocycline	92.5	0	7.5	2	4			
PipTazo	92.5	2.5	5	1	8				
<i>S. marcescens</i> (n=26)	Tigecycline	100	0	0	0.5	1			
	Amikacin	100	0	0	2	2			
	AmoxClav	0	0	100	>32	>32			
	Ampicillin	0	0	100	>32	>32			
	Cefepime	100	0	0	>0.5	>0.5			
	Ceftazidime	100	0	0	>8	>8			
	Ceftriaxone	96.2	3.8	0	0.12	1			
	Imipenem	100	0	0	0.5	1			
	Levofloxacin	96.2	0	3.8	0.06	0.12			
	Minocycline	100	0	0	2	4			
PipTazo	100	0	0	1	4				

Conclusion: Overall, the pathogens analyzed from these three countries are still very susceptible to most broad spectrum antimicrobials. Tigecycline's MIC₉₀ of 0.5 mcg/ml against gram-positive pathogens (including resistant phenotypes) and MIC₉₀ of 0.5 mcg/ml against overall *Enterobacteriaceae* and *Acinetobacter* spp. validate the potent inhibitory activity of TIG against community/hospital pathogens isolated from Switzerland, Sweden and The Netherlands.

INTRODUCTION

Tigecycline (formerly GAR-936) is a member of a new class of antimicrobial agents, the glycyclines. This synthetic analogue of the tetracyclines exhibits significant antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as four-fold better than vancomycin and daptomycin [1, 2]. The development of tigecycline is important in that it is active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. Certain substituents at the 9-position of the tetracycline molecule restore activity against bacteria harboring genes encoding either or both efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic and anaerobic bacteria [3]. Furthermore, resistance to tigecycline is difficult to produce even in the laboratory.

Previous studies have demonstrated excellent in vitro activity for tigecycline against clinical and laboratory strains of gram-positive and -negative bacteria with minimum inhibitory concentrations for the 90th percentile at or below 2 mcg/ml, including difficult to treat methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *enterococci* (VRE) and extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* [4-6]. This study was undertaken to document the in vitro activity of tigecycline against significant numbers of clinical pathogens collected in population centers in Switzerland, Sweden and The Netherlands. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

MATERIALS & METHODS

All isolates were derived from blood, respiratory tract, urine (no more than 25% of all isolates), skin, wound, body fluids, and other defined sources. Only one isolate per patient was accepted into the study. Clinical isolates were collected and tested from 2004 to 2006 from one study center in each of Switzerland, Sweden and The Netherlands. Isolates were identified to the species level and tested at each site by the participating laboratory. Organism collection, transport, confirmation of organism identification, and development and management of a centralized database, were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA. All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory criteria. Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [7]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturer, MicroScan (Dade Behring Inc., Sacramento, CA, USA). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amikacin (0.5-64); amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.5-32, gram-negative panel, and 0.06-16, gram-positive panel); ceftazidime (0.5-8); ceftriaxone (0.06-64); ceftazidime (0.5-32); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [8] and the recent US Food and Drug Administration package insert for tigecycline [9], where applicable.

Escherichia coli, *Klebsiella pneumoniae* and *Klebsiella oxytoca* were screened for ESBL activity when MIC results for ceftriaxone were >1 mcg/ml using broth microdilution panels. ESBL activity was confirmed using the CLSI (2005) phenotypic confirmatory disk test (Oxoid, Ogdensburg, NY, USA) on Mueller-Hinton agar (Remel Inc., Lenexa, KS, USA) according to CLSI (2005) guidelines. ESBL presence was confirmed by testing the following antibiotic disks: cefotaxime (30-mcg), cefotaxime/clavulanic acid (30/10-mcg), ceftazidime (30-mcg), and ceftazidime/clavulanic acid (30/10-mcg). Antimicrobial disks were manufactured by Oxoid, Inc. (Ogdensburg, NY, USA). Mueller-Hinton agar used in testing was manufactured by Remel, Inc. (Lenexa, KS, USA). An organism was interpreted as containing an ESBL if there was an increase of >5 mm in the inhibition zone of the combination disk when compared to that of the cephalosporin alone.

Quality controls (QC) were performed by each testing site on each day of testing using the corresponding ATCC control strains: *E. coli* ATCC 25922; *E. coli* ATCC 35218; *H. influenzae* ATCC 49766; *H. influenzae* ATCC 49247; *S. aureus* ATCC 29213; *Pseudomonas aeruginosa* ATCC 27853; *Enterococcus faecalis* ATCC 29212 and *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2005) guidelines [8].

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The results are listed in the following tables.

Table 1. In vitro activity of tigecycline and comparative agents against *Enterobacteriaceae*.

Organism Name	Drug	%SUS ^a		%INT		%RES		MIC (mcg/ml)	
		%SUS ^a	%INT	%RES	MIC ₅₀	MIC ₉₀	MIC ₉₅		
<i>E. coli</i> (n=73)	Tigecycline	100	0	0	0.12	0.12			
	Amikacin	100	0	0	2	4			
	AmoxClav	99	8.2	2.7	4	16			
	Ampicillin	98.9	0	41.1	4	>32			
	Cefepime	98.9	1.4	2.7	>0.5	>0.5			
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	Imipenem	100	0	0	0.25	0.25			
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<i>S. aureus</i> ^b (n=75)	Tigecycline	100	0	0	0.25	0.5			
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	AmoxClav	0	0	100	>32	>32			
	Ampicillin	0	0	100	>32	>32			
	Cefepime	100	0	0	>0.5	>0.5			
	Ceftazidime	100	0	0	>8	>8			
	Ceftriaxone	97	0	3	>0.06	0.25			
	Imipenem	100	0	0	0.25	0.5			
	Levofloxacin	100	0	0	0.03	0.06			
	Minocycline	100	0	0	1	2			
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<i>E. cloacae</i> (n=40)									